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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/025,514	12/18/2001	Philip J. Barr	368292000200	6421

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EXAMINER	
WALICKA, MALGORZATA A	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 08/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/025,514	BARR ET AL.	
	Examiner	Art Unit	
	Malgorzata A. Walicka	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 12-45* is/are pending in the application.

4a) Of the above claim(s) *3,5-7,9,10,12-15 and 18-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,8 and 42-45* is/are rejected.

7)☒ Claim(s) *4,16,17,36 and 37* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 2, 2005 has been entered.

Claims 1 and 11 were previously cancelled. Claim 8 has been currently amended. New claims 42-45 have been added. Claims 2-10 and 12-45 are pending. Claims 3, 5-7, 9-10, 12-15 and 18-35 are withdrawn form consideration as directed to the non-elected invention. Claims 2, 4, 6, 16, 17, 36, 37 and 42-45 directed to the elected invention are the subject of this Office Action. Claims 26-35 and 38-41 will be consider for rejoinder at such time as allowable composition claims are identified.

Detailed Office Action

1. Rejections

1.1. 35 U.S.C. 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 42-45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are confusing, because they are directed to a fusion protein that comprises at least an elastase inhibitory domain of AAT and at least a trypase inhibitory domain of SLPI. It is not clear what else, except for the domains, said fusion protein contains.

Claims 43-45 are also unclear in reciting the limitations "wherein said fusion protein is capable of inhibiting of neutrophil elastse, trypase, kallikrein, cathepsin G, and mast cell chymase. All these limitations are already implicitly included in claim 2, because these are characteristic features of AAT, and the claimed fusion protein possesses the AAT activity.

1.2. 35 U.S.C. 112, second paragraph

1.2.1. Lack of written description

Claims 42-45 are rejected under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to large and variable genera of fusion proteins, wherein the fusion protein has inhibitor activity of AAT and SLPI and comprises

1) at least the elastase domain of alpha 1-antitrypsion,

2) at least a trypase inhibitory domain, and

The scope of the claims encompasses a large genus of fusion proteins for which

the specification does not provide a support. The language "elastase domain" and "trypase domain" is absent from the disclosure as filed and Applicants do not provide the structural characteristics of the elastase and trypase domains. Thus, the newly submitted claims constitute new matter. In conclusion, due to the lack of sufficient structural of the claimed fusion proteins one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

1.2. Rejection under 35 U.S.C 103

Claim 2 and 8 were previously rejected under 35 U.S.C. 103(a) as being unpatentable over Australian document AU-B-13288/88 with priority date March 20, 1987 as applied to claim 2 above, and further in view of the article by Bingle L. et al., Thorax, Dec. 1996, vol. 51/12, pages 1273-1274.

Traversing this rejection Applicants in their Remarks of August 2, 2005, argue,

> "the Australian patent describes the cloning and gene structure of hLS2. In addition, the Australian patent describes exon swapping of hSL2. However, there is no teaching or suggesting of purely chimeric fusion forming multi-functional protease inhibitors that contain intact protease inhibitor components", Remarks, page 8, line 21.

This argument of Applicants is found not persuasive because the claims are not directed only to a fusion protein comprising two intact protease inhibitors, but also to a

fusion protein comprising fragments of two protease inhibitors. However, upon reconsideration of the Australian Patent, the examiner agrees that its use in the rejection is improper. The construct relied on in the rejection does not contain two protease inhibitors because, as Applicants point out, angiotensin is not an inhibitor. Furthermore the functionality of the construct is not taught by the Australian Patent.

Nevertheless, claims 2, 8, and new claim 42 are rejected 35 U.S.C. 103(a) as being unpatentable over Urwin P. et al, (*Enhanced transgenic plant resistance to nemathodes by dual proteinase inhibitor constructs, Planta*, 1998, 204, 472-479, attached) and WO 92/10575 document published 1992 (attached) in view of the article by Bingle L. et al., (*Secretory leucoprotease inhibitor: partnering alpha 1-proteinase inhibitor to combat pulmonary inflammation, Thorax*, Dec. 1996, vol. 51/12, pages 1273-1274; a copy enclosed to the Office Action of July 22, 2004).

The claims are directed to a fusion protein comprising alpha 1-antitrypsin or a functionally active portion thereof, and secretory leukocyte protease inhibitor or a functionally active portion thereof, wherein said fusion protein has alpha 1-antitrypsin activity and secretory leukocyte protease inhibitor activity or to a fusion protein comprising elastase inhibitory domain of AAT and trypase inhibitory domain of SLPI.

Urwin et al. teach a dual protease inhibitor consisting of full-length cystein (CPT1) and serine protease (Oc-IΔD86) inhibitors from intestines of *Nemathode*. The fusion inhibitor, called Oc-IΔD86/GO/CpT1 was expressed in plant and shown to *in vivo* protected this organism against *Nemathode* infections. The efficiency of protection was

higher than in case when both inhibitors were acting separately. See results in Table 2 and 3 and the comment on page 476 right column above the paragraph **Discussion.** In the comment the authors state that the fusion protein had an additive effect of both protein inhibitors. Thus, Urwin et al. teach that the whole molecules of protease inhibitors can be combined in a fusion protein retaining their activities.

WO documents teaches bifunctional inhibitors of thrombin and platelet activation (disintegrins), wherein said bifunctional inhibitors comprise inhibitory domains of both inhibitors from different sources. The fusion protein is constructed by linking combining N-terminus of one peptide to C terminus of the second peptides or *vice versa* (page 15, line 22). The fusion proteins are set forth by SEQ ID NO: 2-9; see page 22 and further. The document teaches also production of fusion proteins in host cells, purification of the fusion proteins and their use for treating thrombotic disease. The examples of the WO document disclose many activities of the fusion proteins related to thrombosis.

Urwin et al. and WO documents teach that protease inhibitors used as a whole or as as their active fragments may be combined in fusion proteins that retain their inhibitory functions. Neither Urwin nor WO document teach the fusion protein consisting of alpha 1-antitrypsin and secretory leukocyte inhibitor or of their active parts.

Bingle et al. teaches, "SLPI is a significant component of the anti-NE [neutrophil elastase] shield in the lung, which has different reactivity from, and is therefore complementary to, the anti-NE action of α_1-proteinase inhibitor"; see the Abstract. Furthermore, Bingle et al. strongly suggest that secretory leukocyte protease inhibitor and alpha 1-protease inhibitor, i.e. alpha 1-antitrypsin, are the most effective for

treatment of inflammatory lung disorders such as emphysema, bronchiectasis, pulmonary fibrosis, acute lung injury and bronchopulmonary displasia **when used in combination**; see page 1274, the text bridging the left and right column. The "combination" or "partnering", announced in the title, means to associate as a partner, which in the disputable case of use of two proteins includes also their fusion.

It would have been obvious to one having ordinary skill in the art at the time of invention to have a bifunctional fusion protein consisting of full-length protease inhibitors as taught by Urwin et al. or WO fusion protein consisting of the active parts of protease inhibitors and modify them so that they comprised alpha 1-antitrypsin and SLPI or their functionally active parts. The motivation to combine alpha 1-antitrypsion and human secretory leucocyte inhibitor in one fusion protein was provided by Bingle et al., because they teach that combination of both activities as partners is of high therapeutic importance, and a fusion provide the closest partnership. The therapeutic importance of such composition is the greater that the SLPI has also been shown to possess anti–HIV activity at physiological concentrations. Therefore, combining both serpins in one protein would provide a therapeutic fighting a large number of lung disorders including those related to HIV. The expectation of success was very high because Urwin and WO document teach that fusion proteins comprising the full-lengh or functionally active parts of protease inhibitors remain activities of their components.

Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

Traversing rejection over Binble Applicants argue in their current Remarks:

"Applicants submit that this treatment in combinationin no way suggests a fusion protein. As noted previously, applicants respectfully submit that the qualified and conditional nature of Bingle's actual language—'***could prove*** beneficial', '***feasible that*** rSLPI ***could be used***', and '***[p]robably*** the most effective ***would*** entail' fails to provide motivation", page 11the first paragraph.

Applicants' arguments have been fully considered but are found not unpersuasive for the following reasons. As to the Binble's failing to provide motivation, the title is self-evident: "**Secretory leukoprotease inhibitor: <u>partnering</u> alpha 1-proteinase inhibitor to combat pulmonary inflammation** [emphasis added] ". Partnering means to associate as a partner, which in the disputable case of use of two proteins includes their fusion, because the fusion means the closest partnering. Furthermore, it is common in the art that ideas presented in review articles are reduced to practice by skilled artisans.

Furthermore Applicants opinion is, "nothing in Bingle suggests the desirability of so constraining [fusion obligates the administration of the two agents in 1:1 stechiometry, on a common dosage schedule] the clinical administration of these agents. In addition, Bingle comment that SLPI remains potent when oxidized, in contrast to AAT, would suggest that SLPI be less frequently administered, or in lower dosage, than AAT, teaching away from their fusion."

Applicants' position has been fully considered. However, whereas it is true that SLPI remains potent when oxidized in contrast to AAT, the disclosure is silent about oxygen effects on activities of both inhibitors when they are fused. Applicants do not provide any evidence that AAT activity of the fusion protein disappears with time faster than the SLPI activity of the fusion protein. In addition, the pharmacokinetics of both proteins administered separately or as a fusion protein are not taught by Applicants. If the AAT and SLPI should be used as partners, as the Bingle's review suggest, the simplest way to deliver them *in loco* is in the form of a fusion protein. For all the above reasons one skilled in the art cannot accept the notion that Bingle's article teaches away from the claimed invention.

5. Conclusion

As stated in the previous Office Actions, the claims contain allowable subject matter. Claims 4, 16, 17, 36 and 37 are objected to as depending on rejected claim 2 but would be allowable if rewritten in an independent form.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka whose telephone number is (571) 272-0944. The examiner can normally be reached on Monday-Friday from 10:00 a.m. to 4:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Malgorzata A. Walicka, Ph.D.

Art Unit 1652

Patent Examiner

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